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REVIEW

Molecular biology and riddle of cancer: the 'Tom & Jerry' show

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Abstract From the conventional Bird's eye, cancer initiation and metastasis are generally intended to be understood beneath the light of classical clonal genetic, epigenetic and cancer stem cell model. But inspite decades of investigation, molecular biology has shown hard success to give Eagle's eye in unraveling the riddle of cancer. And it seems, tiring Tom runs in vague behind naughty Jerry.

Keywords Molecular biology · Cancer · Epigenetics · Cancer stem cell · Clonal expansion

Introduction

> "…it is necessary to periodically subject to the deepest revision the principles, which were recognized as final and were no longer discussed".
>
> Louis de Broglie

Molecular biology is materialistic in underlying belief [1], where biological organization is determined by linear relationship among DNA, RNA and protein [2]. But there are several evidences available that contradict this linear central dogma of life. Goldschmidt [3] found that at a certain developmental stage, if Drosophila embryos are exposed for short duration to high temperature, X-rays, or other factors; there may be phenotypic alterations that mimic or copy the kind of changes produced by gene mutations and sometimes these changes may be heritable indicating that they are accompanied by genetic mutations. He termed these phenotypic changes which can cause mutations in the encoding genome as 'phenocopy' and this phenomenon is contrary to the linear pattern of DNA–RNA–Protein [1]. Again, the occurrence of adaptive mutations has challenged the neo-Darwinian principle that selection for advantageous mutations directs the evolutionary change where mutations occur randomly [4]. Cairns et al. [5] reported that when the mutant phenotype has clear selective advantage, the specific mutations take place at a much higher rate in bacteria. These adaptive mutations have since been reported in many bacteria and eukaryotes [6–10].

Moreover, the notion that DNA is the complete hereditary determinant is under question by several investigations. DNA polymerase, a nano-biomotor, is subjected to about 3×10^5 computational steps for every DNA base that the motor reads. Each of the internal microscopic states of the protein can store information, and these higher information storage densities cannot be stored in DNA alone [11]. C-value paradox shows that organizational complexity is not determined by the DNA sequence [12], as a simple microorganism may carry larger DNA sequence than complex human. Even the form of an organism may evolve in absence of corresponding molecular evolution in DNA [13, 14]. Thus, the DNA is merely able to transfer the information for the shape of the proteins, not to transfer the information necessary to organize the proteins inside the cell. Experiments showed that *Tetrahymena pyriformis* cells and *T. vorax* microstomes maintain similar morphology with different proteins, while

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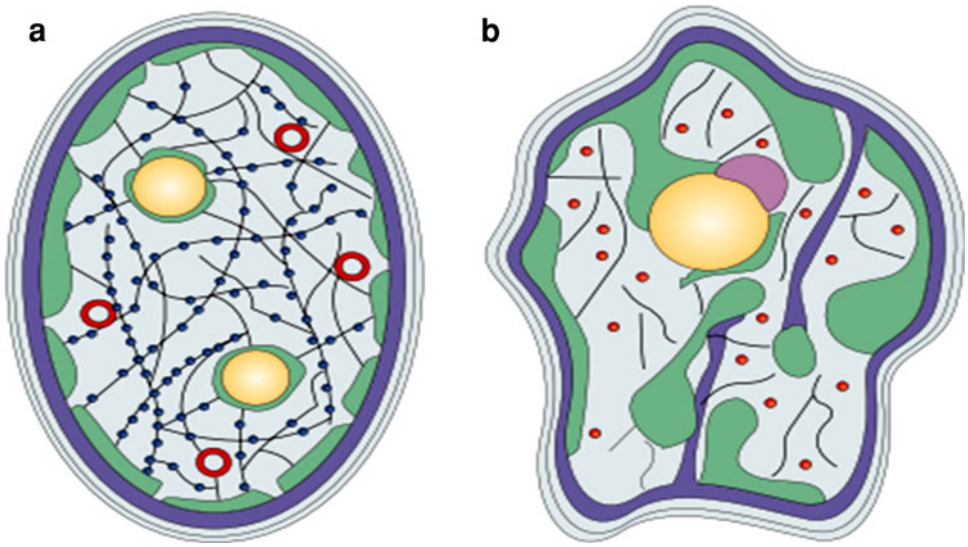

Fig. 1 Nuclear structure in **a** normal cells and **b** cancer cells [24]

T. vorax microstomes and *T. vorax* macrostomes maintain different morphologies with similar proteins and the cellular configuration is not decided by the proteins they consist of [15, 16]. Apparently, the mechanisms behind cell (supra-cellular as well) organization and morphogenesis, thereby seem to be very difficult to describe in terms of a conventional molecular biological frame [17].

Cancer is not a regular type of disease rather a group of disease [18], which could be viewed as an aberrant organ [19] that is characterized through the process of tumorigenesis, whereby cells accumulate mutations in oncogenes or tumor suppressor genes that allow chromosomal aberrations, genomic and proteomic instabilities [20], and ultimately result into abnormal proliferation and differentiation [21]. The organization of cells takes place at different levels from molecules to organelles that again organize to form the full cell, and cell organelles are shaped precisely after the needs of the specific type of cell, e.g., endoplasmic reticule, the golgi apparatus, the vesicle, cell membrane systems, and mitochondrion, that take their shape after the specific type of cell [2]. And cancer cells reorganizes these organelles [22] indicating that basic organizational pattern of the living system may be involved in cancer initiation and progression. Also there are several hints pointing that cancer evolution ascertains non-linearity, geometric alterations in biomolecular arrangement. There are characteristic differences in the nuclear architectures of cancer cells, compared with the normal cells (Fig. 1). Cancer also accelerates the aging process [23] and disrupts the orderliness of the body. These evidences could be the account for both spatial and temporal disorder in cancer.

In molecular biology, it is the common thought that activation of oncogenes or inactivation of tumor suppressor

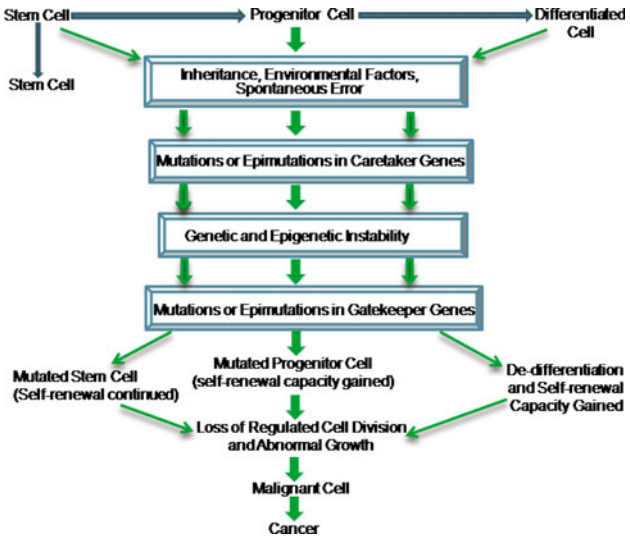

Fig. 2 Unified classical approach for cancer initiation

genes occurs through a point mutation, a deletion or a translocation inside the genome [25]. Clonal expansion model, epigenetic alterations and cancer stem cell model (Fig. 2) have tried to explain cancer initiation and metastasis from the classical view-point. However, our approach is aimed for a brief verification of these existing views from a closer look.

Clonal expansion

There are several genes responsible for controlled growth in human body. Errors in these genes due to germline defects, intrinsic replication errors and environmental mutagens are very general. With age-dependent growth

control, loosen and neoplastic cells may appear, so that a linear multistage model was used to explain the origin of cancer [26, 27]. Mutations in several oncogenes, tumor suppressor genes (TSGs), and genomic stability genes occur in cancer [28]. According to the clonal genetic model, carcinogenesis is a multistage process [29–31] which involves initiation (due to inheritance, environment and spontaneous errors), promotion (due to mutation in oncogenes and tumor suppressor genes), progression (uncontrolled growth) and conversion into neoplastic phenotype (cancer) that can metastasize [29, 32].

A gene increases the response to growth stimulation by a growth factor, inhibits the ability of a stem cell to terminally differentiate or become apoptotic with an initiating mutation, and promoters such as epidermal growth factor (EGF) might induce proliferation selectively in those initiated cells [29]. But there is evidence of carcinogenesis, due to over expression of promoters like EGF where no initial mutation occurred [33]. Again, it is not necessary for oncogenes to perform strictly at the promotional phase of carcinogenesis. It was reported that codon 12 mutations of H-ras oncogene in rat mammary and esophagus tumors were present prior to the tumor formation [34, 35]. Urban et al. [36] showed that K-ras mutations may occur after neoplastic conversion. These findings certainly disrupt the linearity of clonal genetic model. Moreover, most cancer cells are aneuploid and missegregation of chromosomes occur frequently during mitosis, and spindle checkpoint acts as the main cell cycle control mechanism that prohibits chromosomal instability, in normal condition [37]. In the absence of chromosomal instability deletion or alterations in tumor suppressor genes will lead to apoptosis [32]. But mutation or deletion of a major tumor suppressor gene RB should occur in G1 phase in order to continue deregulated cell cycle and tumor suppressor gene CDKN2 is also found deleted in G1 phase of cell cycle [38], while chromosome segregation occurs in mitotis and chromosomal instability might initiate carcinogenesis [39]. So it seems, the process of cancer initiation might be non-linear.

Clonal selection model is a mere assumption [32] which is effective when cells are known in terms of one mutated or altered oncogene at a time. But the fact is, a large number of genetic alterations occur within the same genome to create genetic instability [40]. There are a number of models to explain this complex dynamic process involving caretaker and gatekeeper mutations [39, 41, 42]. So, in the context of cancer cells, this linear clonal expansion or clonal genetic model may be said to be quite obsolete [43] if not immersed with a modern holistic approach for cancer initiation.

Classical epigenetic model

Epigenetics defines the heritable alterations in gene expression without changes in DNA sequence. These alterations include DNA methylation, histone modifications, packaging of DNA around nucleosomes, chromatin folding and attachment to the nuclear matrix [44]. Global DNA hypomethylation, local hypermethylation in promoter region of tumor suppressor genes, alterations in chromatin remodeling, loss of gene imprinting (LOI) are the epigenetic processes which may precede genetic mutations and genomic instability in tumorigenesis [45, 46]. These preceding epigenetic changes in early stages of tumorigenesis in pre-malignant cells of tumor, e.g., lung, colon and prostate tumors might direct the subsequent genetic alterations and help in tumor progression [47–52]. Epigenetics plays a major role in the development and cellular differentiation of an organism, and the alterations in epigenetic processes cause inappropriate gene silencing followed by tumor formation [53, 54].

There is evidence for genetic regulation of epigenetic phenomena. Alterations in this epigenetic gene expression pattern will cause epigenomic instability. DNA methyltransferase (DNMTs), methyl-binding protein (MBDs), histone acetylase (HATs), histone deacetylase (HDACs), histone methylase (HMTs), histone demethylase etc. are epigenetic genes found inside the genome. There may be both germline (high penetrance or low to medium penetrance) and somatic changes in these genes which cause epigenomic alterations in tumorigenesis. For instance, four member of DNMT family: DNMT1, TRDMT1, DNMT3A and DNMT3B are responsible for transferring methyl group to cytosine residues in CpG islands [55]. Germline single nucleotide polymorphisms (SNPs) in DNMT3B have been reported to increase the risk of cancer. One SNP ($-149C > T$) may increase the risk of breast cancer [56], two SNP ($-283T > C$ and $-579G > T$) may increase the risk of lung adeno-carcinoma [57]. DNMT1 inactivation may be associated with tumorigenesis as 2 of 29 colorectal cancer patients showed somatic mutation in DNMT1 [58]. Epigenetic silencing of SFRP gene activates Wnt pathway in early colonic neoplasia. DNMT genes were deleted in colon cancer cell line HCT116. Despite activated β-catenin expression, the cells had shown down regulation of Wnt pathway and apoptosis, because the deletion led to SFRP re-expression through promoter demethylation [59]. This certainly proves the role of epigenetic genes in tumorigenesis which may act as oncogenes or tumor suppressor genes. But the underlying processes causing alterations in epigenetic genes is mostly unknown [55].

Recently, it has been found that small, single stranded micro-RNAs (miRNAs) have regulatory role in gene expression by interfering with mRNAs and also

participates in metabolism, differentiation, cell cycle regulation, development etc. [60, 61]. MiRNAs show similar regulatory mechanisms like protein-coding genes [62]. Most of these miRNAs e.g., miR-1 and miR-34b/c in colorectal cancer, miR-9 in breast cancer, let-7 in colorectal, prostate, lung, breast cancers and hepatocellular carcinoma are epigenetically regulated [63–67]. But a small group of miRNAs called epi-miRNA seems to regulate epigenetic genes such as miR-148a/b targets DNMT3b in cervical cancer [68, 69], miR-449a targets HDAC1 in prostate cancer [70]. There is also evidence for gene introns to produce mi-RNA which are named as intron-derived miRNA (Id-miRNAs), and these Id-miRNAs can regulate gene expression through RNA interference. Altered Id-miRNAs due to changes in intron sequence can cause diseases such as myotonic dystrophy and fragile X syndrome [71]. As large arena of detailed miRNAs and Id-miRNAs function is yet to be elucidated, these molecules may have obvious relation with genetic and epigenetic changes leading to tumorigenesis. There are reports like, miRNA let-7 acts as tumor suppressor in lung cancer while it targets oncogene RAS and miR-21 acts as oncogene in several neoplasm while targeting tumor suppressor PTEN1 and PDCD4 [72]. Gene function competency depends on both faithful transcription of protein-coding genes and controlled spatial and temporal regulation which involves epigenetics [73]. MiRNAs, epi-miRNAs and Id-miRNAs have created new complexities in unraveling the mystery behind cancer initiation.

Cancer stem cells

Tumor sample from different patients and even cells within the same tumor shows significant discrepancy in morphology, proliferative potential, ability for metastasis and invasion as a reflection of variation in genetic and epigenetic aberrations [74]. The ability to form a tumor has been found to be limited within very small proportion of cancer cells. Experiment with neuroblastoma, ovarian and lung cancer had shown that only 1 out of 1–5,000 cancer cells could form colony in soft agar [19]. Malignant cervical epithelial cells express proteins such as nanog, nucleostemin, and musashi1 which are also highly expressed in embryonic stem cells [75]. Widespread potential for proliferation is characteristic of both normal stem cells and tumorigenic cells which make them capable of forming normal and abnormal organs, respectively [21]. From this point of view, we can say cancer is an abnormal organ that exhibits false impression of normal tissue development, where growth is driven by the stem cell apex [76]. Stem cells give rise to off-springs which can either retain stemness similar to the parent through self renewing capacity [19], or can go to differentiation pathway through negative feedback loops (epigenetic switching) repressing the self renewal genes and produce phenotypically diverse transit-amplifying progenitors [77]. A cancer cell carrying these similar properties is termed as cancer stem cell that subsequently produces new cancer stem cells and non-self-renewal progenies which form the bulk of tumor. These non-self-renewal progenies are reactive to therapy while stem cells escape the therapeutic effect and may form tumor anew [46, 78].

Several cancer gene pathways such as Bmi-1, Wnt, Sonic hedgehog (Shh), and Notch may show involvement in the regulation of normal stem cell development, and these self renewal genes were primarily recognized as oncogenes for their role in tumorigenesis [19, 79, 80]. For example, Wnt pathway might have a role in hematopoietic stem cells (HSCs) self renewal [79] as Wnt proteins are found in bone marrow during normal development [81]. In canonical Wnt pathway, binding of Wnt protein with transmembrane receptor protein frizzled results in inactivation of β-catenin degradation complex that comprises GSK3-beta, APC and AXIN. Consequently, stabilized β-catenin translocates to the nucleus and activates TCF transcription factor which activates proto-oncogene CCND1 and C-MYC. In the absence of Wnt signal, β-catenin is tainted by the degradation complex. Disregulated Wnt signaling due to mutations in genes that encode proteins involved in this pathway can cause tumor formation [82]. Aberrant Wnt signaling was seen in various cancer samples such as leukemia, colon cancer, colorectal cancer which might contribute to the self renewal of cancer stem cells [83]. Ability for differentiation and self renewal are the basic criteria of stem cells [74] that need to be balanced in order to maintain a homeostatic stem cell pool [44], and normal tissue organization is determined through tight regulation of stem cell expansion [84, 85]. Morrison et al. [86] have shown multigenic regulation of hematopoietic stem cell (HSC) number in mouse model. Different ways such as oncogenic mutation that causes aberrant expansion of normal stem cell, gaining self renewal capability through oncogene activation that subverts the negative feedback loop in transit-amplifying progenitors, or multiple mutations in differentiated cells allowing de-differentiation can originate cancer stem cell [18, 44]. Aberrant epigenetic switching may transform normal cells into tumorigenic cells [62]. In nude mice, IL6/NF-kB/LIN28B/let-7 positive feedback loop is required to maintain the self renewing capacity of cancer stem cells which were epigenetically transformed due to inflammation [66]. Again through OCT4/SOX2/C-MYC/KLF4 positive feedback loop, adult fibroblast cells can be reprogrammed into stem cell like state [62].

Stem cell microenvironments also have vital role in maintaining self renewal capacity and determining differentiation pattern. Tissue architecture can be maintained even in the presence of transformed cells by a normal microenvironment, while a mutated cell can be triggered to form tumor by aberrant microenvironment [87]. Wnt ligands can be produced from both HSCs and microenvironment [88]. Also there is evidence against cancer stem cell model. Each cancer cell showed stemness in different experimental murine leukemia and cancer stem cell model was strongly questioned [74]. Cancer stem cells have not been broadly studied, so we cannot say it is valid for all human cancers. Though this model seemingly combines the existing knowledge in cancer biology, several questions remain unanswered. How the self renewal in cancer stem cells is regulated? Where the first transforming mutations take place? What is the character played by the microenvironment in the cancer drama? How these genetically unstable abnormal cells with increasing mutations survive and proliferate? Though generally, genetic instability should be expected to cause apoptosis as increasing mutations should parallelly increase the overall likelihood of cellular breakdown [89, 90]. According to clonal selection, cancer cells carrying increasing mutations survive because they have been selected in the evolutionary pathway [41] for their own advantageous characteristics [39, 91]. Selection of a cell means molecular information is conserved during replication but in cancer cells process of replication is abnormal, and more mutations accumulate in the next generation which implies loss or alteration of information [32]. So it might not be realistic to say, cancer initiates through selection of a cell or cell population. Again, Cerny and Quesenberry [92] strongly argued that there is no stem cell-progenitor hierarchy, rather a reversible continuum of shifting chromatin and gene expression with cell cycle transit.

Cancer metastasis

Traditionally, it is well established that metastasis occurs when genetically unstable cancer cells adapt to a tissue microenvironment that is distant from the primary tumor, involving both the selection of traits that are advantageous to cancer cells and the concomitant recruitment of traits in the tumor stroma that accommodate invasion by metastatic cells. It is thought that metastatic cells are selected from genetically diverse progenitors of cancer cells [93], those have accumulated stochastic expression of genes responsible for metastasis [94] and it involves loss of cellular adhesion, increased motility and invasiveness, entry and survival in the circulation, exit into new tissue and eventual colonization at a distant site [94, 95]. But genomic instability that produces heterogeneity for selection is directly driven by mutations [93]. We have already discussed that selection and mutation are in conceptual opposition and it cannot be so easily said that metastatic cells have been selected in the evolutionary pathway. Moreover, metastatic genes have found to be expressed early in tumor's growth [96]. Scott et al. [97] found six abnormal genes that were involved in both cancer initiation and metastasis promotion. So, it may be better to see metastasis as a fate directed by the initiation process rather distinct event caused by the gradual changes.

Conclusions

Basic constraint in biology and medicine is the problem of the connection between subjective and objective factors involved in the process of life [33]. General thought is, genomic instability initiates cancer [39], but distorted centrosome cycle also may cause genomic instability and cancer [98]. DNA and centrosome duplication occur in every cell cycle [99] in coordination and determines the normal run of cell cycle [100]. Both centrosome abnormalities and genomic instabilities are found early in cancer cells [101, 102]; So it is difficult to specify one as primary. Changes in genes such as DNMTs, MBDs, HMTs, HDACs, and HATs, etc. are found to be responsible for characteristic alterations in the so-called cancer epigenome [55]. Together, all these make sense that underlying process of cancer initiation is becoming hazier for materialist molecular biology with classical advances. After all, concepts of oncogenes/tumor suppressor genes have shown hard success to provide any convincing explanation for cancer initiation [98], because each tumor could be distinctive in its genetic makeup and any regular set of gene mutations cannot be accounted with malignancy [103]. Biological molecules act as both specialized chemicals and informational molecules simultaneously. It is analogous to a computer where chemistry corresponds to hardware and information to software, and complete understanding of the way of biological organization requires the explanation of both the hardware and software aspects [104]. Cancer might act as unprecedented and abnormal 'whole' (like organs) in the complex hierarchy of 'wholeness' that works in our body system (cell $<$ organ $<$ organism). This very complex cancer phenomenon, involving so many genes and molecules in the progression of a single tumor, seems to be stochastic by nature, and requires thinking in a way that the alterations are not local, rather the manifestation of the alterations seems to be local and it might be the fact. So, cancer initiation should be viewed from a new holistic paradigm underlying the process of origin and function of life.

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Conflict of interest The authors declare that they have no competing interests.

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